Survival and Prognostic Stratification of 670 Patients With Advanced Renal Cell Carcinoma

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Purpose: **To identify prognostic factors and a model predictive for survival in patients with metastatic renal-cell carcinoma (RCC).**

Patients and Methods: **The relationship between pretreatment clinical features and survival was studied in 670 patients with advanced RCC treated in 24 Memorial Sloan-Kettering Cancer Center clinical trials between 1975 and 1996. Clinical features were first examined univariately. A stepwise modeling approach based on Cox proportional hazards regression was then used to form a multivariate model. The predictive performance of the model was internally validated through a two-step nonparametric bootstrapping process.**

Results: **The median survival time was 10 months (95% confidence interval [CI], 9 to 11 months). Fifty-seven of 670 patients remain alive, and the median follow-up time for survivors was 33 months. Pretreatment features associated with a shorter survival in the multivariate analysis were low Karnofsky performance status (<80%), high serum lactate dehydrogenase (> 1.5 times upper limit of normal), low hemoglobin (< lower limit of normal), high ''corrected'' serum calcium (> 10 mg/dL), and absence of prior nephrectomy. These were used as risk factors to categorize patients into three different groups. The median time to death in the 25% of patients with zero risk factors (favorable-risk) was 20 months. Fifty-three percent of the patients had one or two risk factors (intermediate-risk), and the median survival time in this group was 10 months. Patients with three or more risk factors (poor-risk), who comprised 22% of the patients, had a median survival time of 4 months.**

Conclusions: **Five prognostic factors for predicting survival were identified and used to categorize patients with metastatic RCC into three risk groups, for which the median survival times were separated by 6 months or more. These risk categories can be used in clinical trial design and interpretation and in patient management. The low long-term survival rate emphasizes the priority of clinical investigation to identify more effective therapy.**

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RENAL CELL CARCINOMA (RCC) is the most common tumor arising in the kidney, affecting approximately 30,000 individuals each year in the United States.[1,2] The outlook for patients with distant metastases is poor, with a 5-year survival rate of less than 10% for patients presenting with stage IV disease.[1,2] This reflects the lack of effective systemic therapy for patients with metastases. RCC is resistant to chemotherapy and hormonal therapy because no agent consistently achieves a response in more than 10% of patients.[3] Immunotherapy, ie, interleukin-2 and interferon alpha, achieves responses in 10% to 20% of patients.[1] However, the low response rate, toxicity associated with high-dose regimens,[4] and few long-term survivors after treatment with interferon-alpha or interleukin-2 provide the rationale for clinical trials as a priority for management of patients with this disease.

Determining prognostic factors of survival for patients with advanced RCC would be valuable in directing therapy and interpreting results of clinical trials. Clinical trials in RCC frequently use biologic agents where responses may be delayed for 3 months or more after the institution of therapy,[5] and prospective assessment of patient survival is necessary to determine appropriate eligibility. Response proportions to interferon-alpha, interleukin-2, or combination programs vary considerably among phase II trials,[6] implying patient selection is an important factor in achieving a favorable treatment outcome. Clinical trials that include survival as an end point must account for prognostic factors to assure that treatment groups are comparable so that the proper interpretation of trial outcome can be ascertained. Also, an assessment of patient survival benefits both patient and physician in clinical management.

Published analyses of prognostic factors performed in a multivariate analysis have been limited in both the number of series and the number of patients studied.[7-12] To define pretreatment features predictive of survival, we performed a retrospective study on 670 patients with advanced RCC treated in successive clinical trials at the Memorial Sloan-Kettering Cancer Center (MSKCC). The results were examined by multivariate analysis, and a model was developed to stratify patients according to risk.

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PATIENTS AND METHODS

Patients

All patients were treated on MSKCC Institutional Review Board–approved clinical trials conducted between September 1975 and July 1996. The patients were identified through registration on 24 consecutive MSKCC clinical trials; the specific eligibility and treatment programs have previously been described (Table 1).[13-33] Eligibility details are described in individual reports but all included histologic confirmation of RCC, stage IV disease with presence of measurable lesions, adequate Karnofsky performance status, lack of severe comorbid conditions, and adequate hematologic, renal, and hepatic function.

Patients entered onto more than one clinical trial were evaluated for this study at the time of entry on their first MSKCC trial. Routine studies at the time of clinical trial entry included the following: detailed history and physical examination, complete blood count, prothrombin and partial thromboplastin times, creatinine, total bilirubin, alkaline phosphatase, AST lactate dehydrogenase, blood urea nitrogen, calcium, total protein, albumin, and imaging studies to assess measurable disease. The majority of patients had a computerized tomography scan of the abdomen and chest to assess extent of disease. Response to treatment, time to progression after systemic therapy, and survival and current status were recorded.

Table 1. Composition of MSKCC Retrospective Study

Protocol Reference	Agent(s)	No. of Patients	Accrual Dates
14	Vindesine	18	9/75-5/77
15	Methyl GAG	29	11/79-5/80
16	Flutamide	23	6/80-2/82
17	4-epi-doxorubicin	10	7/80-9/81
18	10-deaza-aminopterin	12	7/80-7/83
*	AAFC*	2	2/81-5/81
19	Bisantrene	18	5/81-10/81
20	4-demethoxydaunorubicin	17	2/82-10/82
13	Interferon-α	36	3/82-4/83
13	Interferon-α	58	7/83-5/84
22	Elliptinium	9	9/83-1/84
21	*N*-methyl-formamide	14	4/84-4/85
13	Interferon-α +/− vinblastine	51	6/84-3/86
23	Trimetrexate	14	9/86-9/87
24	Interleukin-2	68	9/87-3/89
26	Didemnin	20	2/88-9/89
27	Interleukin-2 plus interferon-α	34	7/89-8/90
28	Suramin	21	8/90-6/91
29	Vinblastine	23	6/91-10/93
30	Topotecan	15	12/91-6/92
31	Liposomal doxorubicin	11	9/92-2/94
25	Interferon-α plus 13-cis-retinoic acid	40	1/93-4/94
32†	Interferon-α +/− 13-cis-retinoic acid	109	4/94-7/96
33	13-cis-retinoic acid	18	6/94-2/95

Abbreviations: AAFC, 2′2-anhydro-1-B-D-arabino-F-fluorocytosine; Methyl GAG, methylglyoxal bis(guanylhydrazone)dihydrochloride.

*Trial unpublished.

†Only patients treated at MSKCC included; patients treated by Eastern Cooperative Oncology Group were used as an external validation set and are described in a separate publication.

Table 2. Patient Characteristics

Characteristic	No. of Patients	%	Range
No. of patients	670		
Sex			
Male, %	450	67	
Female, %	220	33	
Age, years			
Median	58		
Range	18-82		
Range of diagnosis dates	6/15/57-6/3/96		
Karnofsky performance status, %			
$\leq$ 60	46	7	
70	146	22	
80	211	32	
90	264	39	
Prior therapy, %			
Nephrectomy	434	65	
Radiation therapy	150	22	
Immunotherapy	56	8	
Chemo- or hormonal therapy	65	10	
No. of metastatic sites, %			
Renal primary or local recurrence only	19	3	
1	242	36	
2	253	38	
3	110	16	
$\geq$ 4	46	7	
Sites of metastatic disease, %			
Lung	483	72	
Mediastinum	135	20	
Retroperitoneal lymph nodes	134	20	
Bone	176	26	
Liver	130	19	
Median baseline laboratory parameters			
Albumin, normal 4.0-5.7 g/dL	4		2.3-5.3
Alkaline phosphatase, normal 0-115 U/L	108		37-1248
Calcium, normal 8.5-10.5 mg/dL	9.7		6.8-14.6
Corrected calcium, normal $<$ 10 md/dL	9.3		6.2-14.2
Hemoglobin, normal $>$ 13 g/dL (M); $>$ 11.5 g/dL (F)	12.3		5.2-18
Lactate dehydrogenase, normal $<$ 200 U/L	189		59-5380

Survival Analysis

The end point of interest was survival time, defined as the time from treatment initiation to the death date or last follow-up date. Clinical features examined included number and sites of metastases (lung, mediastinum, bone, liver, and retroperitoneum), Karnofsky performance status, prior treatment (radiation, chemotherapy, and immunotherapy), prior nephrectomy, the time interval from diagnosis to the start of treatment, and selected baseline biochemical features. The biochemical features were based on a previous analysis and consisted of hemoglobin, serum albumin, alkaline phosphatase, lactate dehydrogenase, and total calcium concentrations.[34] To separate out the effects of

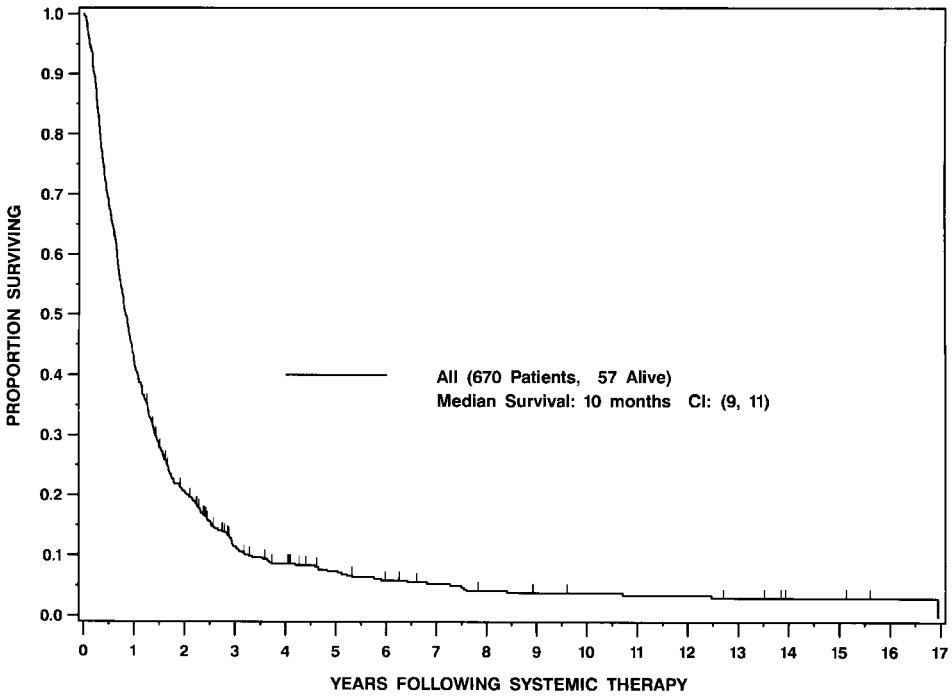

Fig 1. Overall survival (670 patients, 57 alive). Vertical lines indicate last follow-up.

protein binding and assess free calcium, an adjustment formula was used: ''Corrected'' calcium = total calcium − 0.707 [albumin-3.4].[35] The ''corrected'' calcium value was used in the survival analyses.

Survival distributions were estimated using the Kaplan-Meier method.[36] The relationship between survival and each of the variables was analyzed using the log-rank test[37] for categorical variables and a score test based on Cox proportional hazards regression model[38] for continuous variables. Bivariate relationships among the variables were explored to better understand how the variables interacted and how these interactions related to survival. There were few missing values for any of the variables (no more than 2%), and in all analyses, case deletion was used to handle the missing values. When necessary, a logarithmic transformation was used to reduce skewness.

Two types of exploratory plots were used to display the functional relationship between continuous covariates (eg, lactate dehydrogenase and hemoglobin) and patient survival. The first was the running median survival time plot,[39] which divided the covariate values into overlapping intervals, calculated the Kaplan-Meier–based median survival time for corresponding patients, and plotted these median survival times against the midpoint of the intervals. The second was the predictive failure time plot,[40] which plotted the predicted median survival time based on a Cox regression model against each of the observed covariate values. These two plots are more descriptive of the relationship between a continuous covariate and survival time than a Kaplan-Meier plot. They allow the risk of death to vary according to the value of the covariate instead of assuming that all individuals in one group are at an equivalent risk of death.

Multivariate Model

Using a significant relationship with survival as criteria for including a variable in the stepwise modeling procedure, seven variables were retained and entered into a multivariate model. Because this retrospective study included patients in clinical trials from 1975 through 1996, whose treatment included both cytotoxic therapy and immunotherapy, a stratified Cox proportional hazards model[41] was used to account for differences in the year of treatment and the type of therapy. This model states that the hazard or risk of death at time t for a patient in strata j with variables $x = (x_{1j}, x_{2j}, \ldots, x_{pj})$ is

$$\lambda_j(t,x) = \lambda_{oj}(t) \exp(\beta_1 x_{1j} + \beta_2 x_{2j} + \ldots + \beta_p x_{pj})$$

where $\lambda_{0j}(t)$ is the baseline hazard function for strata j and $\beta_1, \beta_2, \ldots, \beta_p$ are the regression coefficients. According to this model, when the regression coefficient is positive, then the risk of death increases with higher values of the variable. When the regression coefficient is negative, the risk of death decreases with higher values of the variable. Using a stepwise modeling algorithm with a .15 significance level for entering and removing explanatory variables, the independent risk factors were determined and the model was formed.

Because it was desired to dichotomize the continuous variables chosen in the modeling for ease of clinical use, a minimum *P* value approach as well as the above exploratory plots were used to perform a cut point analysis.[42] In the minimum *P* value approach, selected values of the prognostic factor are examined as candidates for the cut point. The value is chosen that best separates patient outcomes according to a maximum χ^2 statistic and minimum *P* value or a maximum relative risk. The *P* value is adjusted to account for the problem of multiple testing. The running median survival time plot and predicted failure time plot were used to restrict a region for the cut point search. Laboratory information about biologic cut points coupled with the information from the statistical techniques guided the decision about which cut point to use for each of the variables. It was verified that the relationship between survival and the prognostic factor remained significant when the variable was dichotomized.

Table 3. Univariate Survival Analysis of Number and Sites of Metastases and Prior Therapy

	%	% Alive	Median Survival	CI	χ^2	*P*	Risk Ratio
Clinical features of metastatic disease							
Lung metastases							
Yes	72	8	9.9	8.8-11.0	1.79	.181	1.1
No	28	9	10.6	8.5-13.1			
Mediastinum metastases							
Yes	20	6	11.6	9.4-14.5	0.28	.596	0.9
No	80	9	9.5	8.7-10.7			
Retroperitoneal metastases							
Yes	20	7	8.5	7.7-10.4	1.50	.221	1.1
No	80	9	10.5	9.4-11.6			
Bone metastases							
Yes	26	7	9.0	7.8-11.4	2.42	.120	1.2
No	74	9	10.3	9.2-11.5			
Hepatic metastases							
Yes	19	5	7.4	5.5-8.7	9.00	.003	1.4
No	81	9	10.7	9.6-11.8			
Total no. of metastatic sites							
0 or 1	39	10	10.7	9.2-13.0	3.98	.046	1.2
≥ 2	61	8	9.4	8.4-10.9			
Prior therapy							
Prior radiation							
Yes	22	3	8.2	7.6-9.5	7.59	.0059	1.3
No	78	10	10.7	9.5-11.9			
Prior immunotherapy							
Yes	8	4	8.2	6.2-12.1	0.30	.5863	1.1
No	92	9	10.3	9.2-11.1			
Prior chemotherapy							
Yes	10	8	5.8	4.2-8.0	13.49	.0002	1.6
No	90	9	10.6	9.5-11.5			
Prior nephrectomy							
Yes	65	11	11.3	9.5-12.7	30.40	.0001	1.6
No	35	4	8.3	6.9-10.0			
Interval from initial diagnosis to treatment, years							
< 1	63	6	8.5	7.6-9.4	33.74	.0001	1.6
≥ 1	37	13	13.8	11.8-16.4			
< 2	85	6	8.8	7.9-9.8	30.28	.0001	1.7
≥ 2	25	15	15.1	12.0-18.9			

The categorical counterparts of the risk factors determined in the model were used to assign each patient to one of three risk groups: those with zero risk factors (favorable-risk), those with one or two (intermediate-risk), and those with three or more (poor-risk). Survival curves for each of these groups were estimated, and the groups were compared using the log-rank test.

Validation of Model by Bootstrap Technique

The predictive performance of the model was internally validated through a two-step nonparametric bootstrapping process.[43] In the bootstrap procedure, the original set of data of size N becomes a parent population from which samples of size N are randomly drawn with replacement. In the first step of internal validation, the bootstrapping technique was used for variable selection. Two hundred bootstrap samples were created, and a stepwise procedure was applied to each sample using the same significance level for entering and removing a variable as in the original model. From this analysis, the percentage of samples for which each variable was included in the model from the 200 samples was calculated. Percent inclusion was used to determine the prognostic importance of a variable because it was expected that a prognostically important variable would be included in the model for a majority of the bootstrap samples. A model was formulated that included all variables whose percent inclusion was greater than or equal to 65%.[44] The models obtained from the stepwise modeling algorithm and the bootstrapping technique were compared.

In the second internal validation step, the bootstrap was used for parameter estimation. Three hundred bootstrap samples were created, and, for each of the samples, the model with the five final variables was refit and the regression parameters and risk ratios were estimated. The sample mean and SD of the 300 risk ratios for each parameter were computed and used to formulate confidence intervals about the risk ratio. These estimates were compared with those quantities obtained in the final Cox model.

Table 4. Univariate Survival Analysis of Performance Status and Biochemical Parameters

	Continuous Form		Categorical Form			
	Parameter Estimate	*P*	Cut Point Used	χ^2	Risk Ratio	95% CI
Karnofsky performance status	−0.0458	.0001	< 80	73.62	2.15	1.80-2.55
Albumin	−0.798	.0001	4 g/dL	82.05	2.12	1.80-2.50
Alkaline phosphatase	0.002	.0001	88/115 U/L*	25.42	1.51	1.29-1.78
Hemoglobin	−0.253	.0001	13 g/dL (M)/11.5 g/dL (F)	88.13	2.19	1.86-1.78
Lactate dehydrogenase	0.001	.0001	300 U/L†	105.14	3.32	2.64-4.18
Calcium	0.092	.1274	9 or 11 mg/dL‡	28.69	1.77	1.44-2.18
Corrected calcium	0.373	.0001	10 mg/dL	37.59	1.98	1.59-2.46

*Eighty-eight units per liter used for patients ≤ 55 years old at start of treatment and 115 U/L for patients > 55 years old.

†LDH categorized as 1.5 times upper limit of normal.

‡High-risk group defined as < 9 or > 11 mg/dL.

RESULTS

Patient Characteristics and Treatment

The median age of the patient group was 58 years; 67% were male (Table 2). Sixty-five percent had undergone a prior nephrectomy, 61% had two or more sites of metastases, 22% had received prior radiation therapy, and 18% had received prior immunotherapy or cytotoxic chemotherapy. Thirty-seven percent of patients had an interval from diagnosis to treatment of 1 year or more. Six hundred eight patients (91%) were treated at MSKCC, whereas 62 (9%) were treated at an outside hospital on an MSKCC trial. Treatment consisted of immunotherapy in 396 patients (59%) and chemotherapy (or hormonal therapy) in 274 patients (41%) (Table 1). With regard to immunotherapy, 294 patients were treated with interferon alpha, 68 patients with interleukin-2a, and 34 patients with a combination program. The overall response rate for the 670 patients was 12.5%, which included 10 complete responses and 41 partial responses.

Survival Distribution

The median overall survival time was 10 months (95% confidence interval [CI], 9 to 11 months) (Fig 1). Fifty-seven (8%) of the 670 patients remained alive and the median follow-up time for the survivors was 33 months (range, 0.9 to 187 months). The percentage of patients surviving at 1 year was 42%; the 2- and 3-year survival percentages were 20% and 11%, respectively.

Univariate Survival Analysis

Factors considered in the univariate analyses included number and site of metastases, prior therapy, Karnofsky performance status, and baseline biochemical parameters (Tables 3 and 4). Factors associated with an adverse prognosis included presence of hepatic metastasis, two or more sites of metastases, a Karnofsky performance status less than 80, prior radiation or chemotherapy, lack of prior nephrectomy, and a time interval from disease diagnosis to treatment of less than 1 year. The median survival time according to Karnofsky performance status was 2.7 months for 60%, 6.1 months for 70%, 10.6 months for 80%, and 14.4 months for 90% ($P < .0001$).

The first two columns of Table 4 list parameter estimates and *P* values for testing the association of each biochemical parameter (in its continuous form) with survival. The negative regression coefficients on Karnofsky performance status, serum albumin, and hemoglobin concentrations indicate that, as the values of these three covariates increased, the risk of death decreased. The positive regression coefficients on the other variables indicate that the risk of death increased as the value of the covariate increased. The biochemical parameters found to be significant for an adverse prognosis included low serum albumin, elevated serum alkaline phosphatase, low hemoglobin, an elevated serum lactate dehydrogenase level, and a high corrected serum calcium level. For lactate dehydrogenase, a logarithmic transformation was used to reduce skewness.

The effect on survival of the treatment year and program was evaluated (Table 5). Patients were classified according to treatment with immunotherapy, ie, interferon alpha and/or interleukin-2a, versus chemotherapy (cytotoxics or hormonal therapy) and according to when they received treatment (1975 to 1980, 1981 to 1990, 1991 to 1996). Survival

Table 5. Effect of Agent and Year of Treatment

	No. of Patients	No. of Patients Alive	Median Survival (months)	CI (months)
Agent				
IFNα/IL-2	396	48	12.9	11.5-14.6
Chemotherapy	274	9	6.3	5.1-7.6
Year of treatment				
1975-1980	66	1	4.2	3.3-5.7
1981-1990	370	20	9.4	8.1-10.7
1991-1996	234	36	13.2	11.3-15.2

Abbreviations: IFNα, interferon alfa; IL-2, interleukin-2.

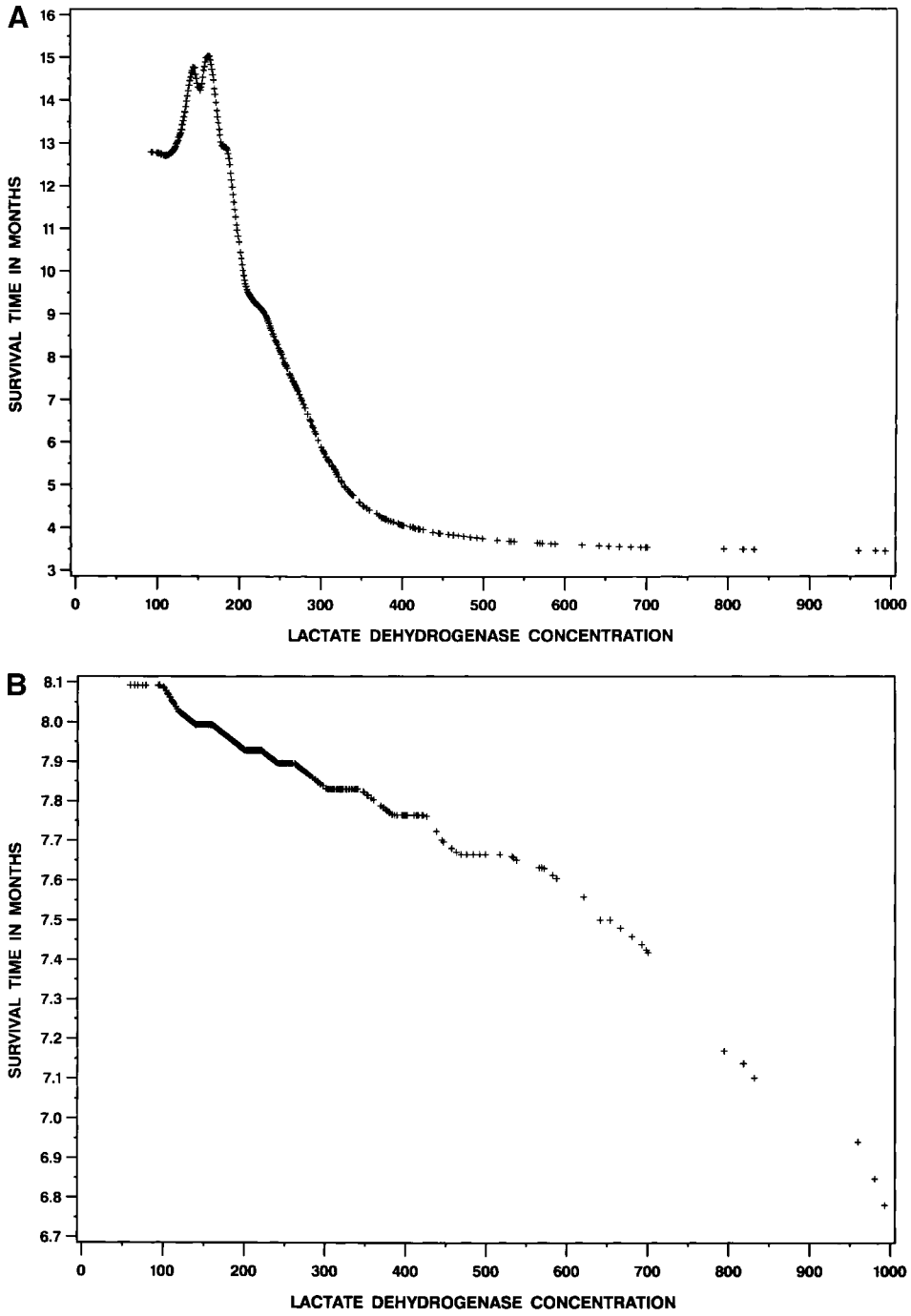

Fig 2. (A) Running median survival time plot and (B) predicted failure time plot for serum lactate dehydrogenase concentration.

was greater for patients treated with immunotherapy ($P < .0001$) and for patients treated in more recent years ($P < .0001$). To account for these effects and to develop a prognostic model based on pretreatment features, type and year of treatment were included as strata in the multivariate survival analysis.

Multivariate Survival Analysis

The seven variables included in the multivariate analysis were hemoglobin, serum lactate dehydrogenase, corrected calcium, prior nephrectomy, Karnofsky performance status, hepatic metastases, and the interval from diagnosis to treatment. Using a .15 significance level for entering and

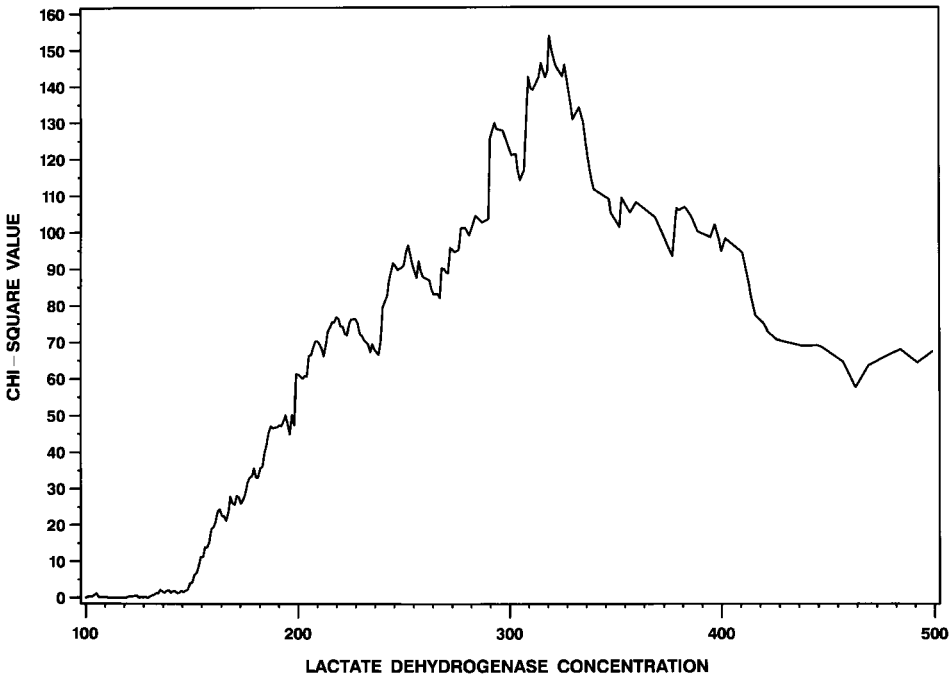

Fig 3. Minimum *P* value approach for lactate dehydrogenase.

removing explanatory variables, it was determined that hemoglobin, lactate dehydrogenase, corrected calcium, nephrectomy, and Karnofsky performance status were independent risk factors predicting survival.

Cut Point Analysis

For hemoglobin and corrected calcium, the cut point suggested by the minimum *P* value approach matched the upper/lower limit of normal. For these variables, the running median survival time plot and predicted failure time plot were continuously increasing or decreasing (monotonic) and did not indicate any obvious cut point. For lactate dehydrogenase, these two plots suggested that its relationship to survival was essentially monotonically decreasing, but that a cut point search could be restricted to values between 100 and 500 U/L (Figs 2A and 2B). The graph from the minimum *P* value approach showed a peak at 319 U/L with a maximum χ^2 value of 153.8 and a minimum *P* value of $< .0001$ (Fig 3). The adjusted *P* value remained significant; therefore, serum lactate dehydrogenase was categorized at the value of 300 U/L (1.5 times upper limit of the normal value).

Table 6. Results of Multivariate Analysis

	Parameter Estimate	SE	χ^2	*P*	Risk Ratio	95% CI
Lactate dehydrogenase	0.9019	0.1230	53.74	.0001	2.46	1.94-3.14
Hemoglobin	0.5439	0.0897	36.75	.0001	1.72	1.45-2.05
Corrected calcium	0.5268	0.1147	21.11	.0001	1.69	1.35-2.12
Karnofsky performance status	0.4050	0.0967	17.56	.0001	1.50	1.24-1.81
Prior nephrectomy	0.2992	0.0908	10.87	.001	1.35	1.13-1.61

No. of Risk Factors	% of Patients	% of Patients Alive	Median Survival (months)	95% CI	1-Year Survival (%)	3-Year Survival (%)
0	25	18	19.9	17.1-27.9	71	31
1 or 2	53	7	10.3	8.9-11.4	42	7
3, 4, or 5	22	0.7	3.9	3.4-5.0	12	0

The last three columns of Table 4 list the cut points chosen for each of the continuous variables along with the results of the univariate survival analysis for the dichotomized versions of the variables. The magnitudes of the χ^2 and the corresponding risk ratio illustrate the magnitude of the covariate's effect on survival. For example, the risk ratio for lactate dehydrogenase was 3.3. This indicates that a patient with a lactate dehydrogenase value greater than 300 U/L was 3.3 times more likely to die than a patient with a value less than 300 U/L. All dichotomized biochemical parameters were significant at the .0001 level.

Risk Groups

Low Karnofsky performance status ($< 80\%$), high lactate dehydrogenase (> 1.5 times upper limit of normal), low serum hemoglobin ($<$ lower limit of normal), high corrected serum calcium (> 10 mg/dL), and absence of nephrectomy were risk factors. Using the dichotomized versions of these

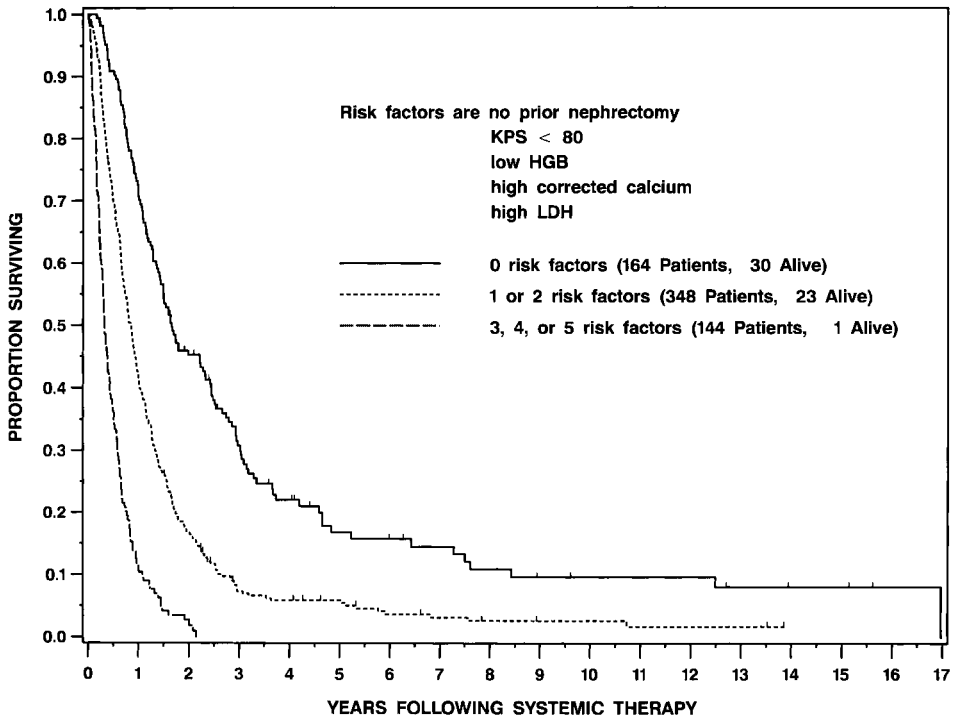

Fig 4. Survival stratified according to risk group (n = 656; 14 patients missing one or more of the five risk factors were excluded). Vertical lines indicate last follow-up.

variables, a Cox model was fit (Table 6). Each patient was then assigned to one of three risk groups: those with no risk factors (favorable-risk), those with one or two risk factors (intermediate-risk), and those with three or more risk factors (poor-risk).

The median time to death in 25% of patients deemed favorable-risk was 20 months, and the 1-, 2-, and 3-year survival rates were 71%, 45%, and 31%, respectively. Fifty-three percent of the patients were in the intermediate-risk group. The median survival time for this group was 10 months, with 1-, 2-, and 3-year survival rates of 42%, 17%, and 7%, respectively. In contrast, the poor-risk group, which comprised 22% of the patients, had a median survival time of 4 months, with 1-, 2-, and 3-year survival rates of 12%, 3%, and 0%. Only one poor-risk patient remained alive at the time of last follow-up. There was a significant difference in the survival profiles of the three risk groups ($P < .0001$) (Fig 4).

Table 7. Percent Inclusion of Each Variable in Variable Selection Step of Bootstrap Validation

HgB	LDH	Corrected Calcium	Nephrectomy	KPS	Hepatic Metastases	Time from Diagnosis to Treatment
100	100	100	67	89	40.5	55

Abbreviations: HgB, hemoglobin; LDH, lactate dehydrogenase; KPS, Karnofsky performance status.

Type and year of treatment were included as strata in the multivariate survival analysis. When patients were stratified according to risk, the median survival time was greater in each of the three risk groups for patients treated in more recent years versus those treated earlier. The median survival time was also greater for patients treated with immunotherapy versus those treated with chemotherapy. For patients treated with immunotherapy (interferon and/or interleukin-2), the median survival times for favorable-risk, intermediate-risk, and poor-risk patients were 26 months, 12 months, and 6 months, respectively.

Bootstrap Validation

In the bootstrap procedure, the original set of data of size N becomes a parent population from which samples of size N are randomly drawn with replacement. The bootstrap samples are then treated as if they come from the true distribution of advanced RCC patients, and inferences about the risk ratios for each covariate are based on the empirical

Table 8. Results of Parameter Estimation Step of Bootstrap Validation

	Risk Ratio	SE	95% CI
Lactate dehydrogenase	2.52	0.3879	1.76-3.28
Hemoglobin	1.76	0.1690	1.43-2.09
Corrected calcium	1.70	0.1989	1.32-2.09
Karnofsky performance status	1.53	0.1656	1.20-1.85
Prior nephrectomy	1.35	0.1375	1.08-1.62

distribution of the risk ratios. For the first step of validation, five of the seven variables had a percent inclusion greater than 65% (Table 7). These were hemoglobin, lactate dehydrogenase, corrected calcium, prior nephrectomy, and Karnofsky performance status. The results of this model selection technique confirmed the variables chosen in the original modeling procedure.

In the second step of validation, a risk ratio with a 95% confidence interval was estimated for each covariate in the final model. Risk ratios (Table 8) were similar to those obtained in the original multivariate model (Table 6). For example, the risk ratio for Karnofsky performance status from the bootstrap procedure was 1.53 (1.20 to 1.85), whereas in the original model it was 1.50 (1.24 to 1.81). The results of these two steps provide evidence of the predictive ability of the final model.

DISCUSSION

This study resulted in a model based on five pretreatment clinical features that predicted survival for patients with advanced RCC. Risk factors associated with a shorter survival period were low Karnofsky performance status ($< 80\%$), high lactate dehydrogenase (> 1.5 times upper limit of normal), low serum hemoglobin ($<$ lower limit of normal), high corrected serum calcium (> 10 mg/dL), and absence of prior nephrectomy. These risk factors were used to stratify patients into three different groups. Three-year survival percentages for the favorable-risk (no risk factors), intermediate-risk (one or two risk factors), and poor-risk (three or more risk factors) groups were 31%, 7%, and 0%, respectively.

Validation was performed by the bootstrap method.[43] Repeated sampling of the original data with replacement allowed independent samples of RCC patients to be generated from which the predictive accuracy of the model was assessed. In addition, we have applied the prognostic model to an external data set taken from a trial by Eastern Cooperative Oncology Group.[32] The external group was composed of 175 patients treated on a randomized trial of interferon-alpha with or without 13-cis-retinoic acid. In this group, the median survival times of favorable-, intermediate-, and poor-risk patients were 29, 14, and 4 months, respectively.

There are few reports of prognostic factors studied by multivariate analysis in patients with metastatic RCC.[7-11,45-50] The prognostic factors vary among the studies but consistently include performance status, nephrectomy, and a measure of extent of disease. A summary of multivariate analyses resulting in criteria for risk stratification is listed in Table 9.[7-12]

A study by Elson et al[7] contained a number of patients similar to the retrospective study in this article. The population was composed of 610 patients treated with chemotherapy on phase II trials between 1975 and 1984.[7] The lack of patients treated with immunotherapy in this analysis[7] is seen by some as a present-day limitation.[9] The model stratified patients into five categories with a difference in median survival time of as little as 1.3 months between groups and included subjective criteria of ''weight loss in previous 6 months'' as a component. Today the patient population is different from that of Elson et al's[7] study, reflecting improvement in imaging techniques and selection factors used to choose patients with RCC exclusively for phase II trials of cytotoxic agents. The median survival time for all patients treated in that series was 5.6 months,[7] compared with 10 months in the present series. Also, the median survival time in the most favorable risk group was 12.8 months, which comprised 18% of the entire group,[7] compared with a

Table 9. Multivariate Analyses of Prognostic Factors for Survival in Patients With Advanced Renal Cell Carcinoma

Author(s)	Year	No. of Patients	Treatment	Independent Pretreatment Prognostic Factors Used in Model
Elson et al[7]	1988	610	Chemotherapy	Karnofsky performance status, time from initial diagnosis, number of metastatic sites, prior chemotherapy, and prior weight loss
DeForges[8]	1988	134	Chemotherapy and interferon-α	Hepatic metastasis, lung metastasis, time from initial diagnosis, sedimentation rate, weight loss
Palmer et al[9]	1992	327	Interleukin-2	Karnofsky performance status, time from initial diagnosis, number of metastatic sites
Jones et al[10]	1993	387	Interleukin-2	Karnofsky performance status, number of metastatic sites, time from initial diagnosis
Fossa et al[12]	1994	295	Interferon + chemotherapy	Karnofsky performance status, sedimentation rate, weight loss
Lopez-Hannineh et al[11]	1996	215	Interleukin-2 with/without interferon-α, 5-FU	Erythrocyte sedimentation rate, lactate dehydrogenase concentration, neutrophil count, hemoglobin, extrapulmonary metastases
Present series	1998	670	Interferon-α, interleukin-2, chemotherapy	Nephrectomy, Karnofsky performance status, hemoglobin, adjusted calcium, lactate dehydrogenase

Abbreviation: FU, fluorouracil.

median survival time of 20 months for favorable-risk patients who participated in the study reported in this article.

The model reported in this article categorized patients into three distinct groups with median survival times of 20, 10, and 4 months. The criteria was based on history of nephrectomy, performance status obtained at physical examination, and assessment of hemoglobin, lactate dehydrogenase, calcium, and albumin (to assess corrected calcium) performed as routine blood tests. Nephrectomy was not performed for the purpose of cytoreduction before the start of systemic therapy. The patient population was selected by fulfilling individual protocol eligibility criteria. For example, patients with brain metastases were excluded. However, the experience was comprehensive, represented a 21-year effort at our center, and included patients treated on clinical trials with cytotoxic, hormonal, and immunotherapies.

In conclusion, five prognostic factors for predicting survival were identified in patients with stage IV RCC selected for clinical trials and used to categorize patients into three risk groups, for which the median survival times were separated by 6 months or more. The 2-year survival rates for patients meeting favorable-, intermediate-, and poor-risk criteria were 45%, 17%, and 3%, respectively. These risk categories can be used in clinical trial design and interpretation, as well as in clinical management. The low percentage of patients achieving long-term survival emphasizes the priority of clinical investigation to identify more effective therapy.

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REFERENCES

1. Motzer RJ, Bander NH, Nanus DM: Renal-cell carcinoma. N Engl J Med 335:865-875, 1996

2. Motzer RJ, Russo P, Nanus DM, et al: Current Problems in Cancer: Renal Cell Carcinoma. St Louis, MO, Mosby, 1997, pp 189-232

3. Motzer RJ, Vogelzang NJ: Chemotherapy for renal cell carcinoma, in Raghaven D, Scher HI, Leibel SA, et al (eds): Principles and Practice of Genitourinary Oncology. Philadelphia, PA, Lippincott-Raven, 1997, pp 885-896

4. Rosenberg SA, Lotze MT, Muul LA, et al: A progress report of the treatment of 157 patients with advanced cancer using lymphokine-activated killer cells and interleukin-2 or high-dose interleukin-2 alone. N Engl J Med 316:889-897, 1987

5. Wirth MP: Immunotherapy for metastatic renal cell carcinoma. Urol Clin North Am 20:283-295, 1993

6. Vogelzang NJ, Lipton A, Figlin RA: Subcutaneous interleukin-2 plus interferon alfa-2a in metastatic renal cancer: An outpatient multicenter trial. J Clin Oncol 11:1809-1816, 1993

7. Elson PJ, Witte RS, Trump DL: Prognostic factors for survival in patients with recurrent or metastatic renal cell carcinoma. Cancer Res 48:7310-7313, 1988

8. De Forges A, Rey A, Klink M, et al: Prognostic factors of adult metastatic renal cell carcinoma: A multivariate analysis. Semin Surg Oncol 4:149-154, 1988

9. Palmer PA, Vinke J, Philip T, et al: Prognostic factors for survival in patients with advanced renal cell carcinoma treated with recombinant interleukin-2. Ann Oncol 3:475-480, 1992

10. Jones M, Selby P, Franks C, et al: The impact of interleukin-2 on survival in renal cancer: A multivariate analysis. Cancer Biother 8:275-288, 1993

11. Hanninen EJ, Kirchner H, Atzpodien J: Interleukin-2 based home therapy of metastatic renal cell carcinoma: Risks and benefits in 215 consecutive patients. J Urol 155:19-25, 1996

12. Fossa SD, Kramer A, Droz JP: Prognostic factors and survival in patients with metastatic renal cell carcinoma treated with chemotherapy or interferon-alpha. Eur J Cancer 30A:1310-1314, 1994 (suppl)

13. Minasian LM, Motzer RJ, Gluck L, et al: Interferon alfa-2a in advanced renal cell carcinoma: Treatment results and survival in 159 patients with long-term follow-up. J Clin Oncol 11:1368-1375, 1993

14. Wong PP, Yagoda A, Currie VE, et al: Phase II study of vindesine sulfate in the therapy for advanced renal carcinoma. Cancer Treat Rep 61:1727-1729, 1977

15. Zeffren J, Yagoda A, Watson RC, et al: Phase II trial of methyl-GAG in advanced renal cancer. Cancer Treat Rep 65:525-527, 1981

16. Ahmed T, Benedetto P, Yagoda A, et al: Estrogen, progesterone, and androgen-binding sites in renal cell carcinoma: Observations obtained in phase II trial of flutamide. Cancer 54:477-481, 1984

17. Benedetto P, Ahmed T, Needles B, et al: Phase II trial of 4′epi-adriamycin for advanced hypernephroma. Am J Clin Oncol 6:553-554, 1983

18. Scher HI, Yagoda A, Ahmed T, et al: Phase II trial of 10-deazaaminopterin for advanced hypernephroma. Anticancer Res 4:409-410, 1984

19. Scher HI, Schwartz S, Yagoda A, et al: Phase II trial of bisantrene for advanced hypernephroma. Cancer Treat Rep 66:1653-1655, 1982

20. Scher HI, Yagoda A, Ahmed T, et al: Phase-II trial of 4-demethoxydaunorubicin (DMDR) for advanced hypernephroma. Cancer Chemother Pharmacol 14:79-80, 1985

21. Sternberg CN, Yagoda A, Scher HI, et al: Phase II trial of N-methylformamide for advanced renal cell carcinoma. Cancer Treat Rep 70:681-682, 1986

22. Sternberg CN, Yagoda A, Casper E, et al: Phase II trial of elliptinium in advanced renal cell carcinoma and carcinoma of the breast. Anticancer Res 5:415-417, 1985

23. Sternberg CN, Yagoda A, Scher H, et al: Phase II trial of trimetrexate in patients with advanced renal cell carcinoma: Clinical Community Oncology Program. Eur J Cancer Clin Oncol 25:753-754, 1989

24. Law TM, Motzer RJ, Mazumdar M, et al: Phase III randomized trial of interleukin-2 with or without lymphine-activated killer cells in the treatment of patients with advanced renal cell carcinoma. Cancer 76:824-832, 1995

25. Motzer RJ, Schwartz L, Law TM, et al: Interferon alfa-2a and 13-*cis*-retinoic acid in renal cell carcinoma: Antitumor activity in a phase II trial and interactions in vitro. J Clin Oncol 13:1950-1957, 1995

26. Motzer RJ, Scher H, Bajorin D, et al: Phase II trial of Didemnin B in patients with advanced renal cell carcinoma. Invest New Drugs 8:391-392, 1990

27. Ilson DH, Motzer RJ, Kradin RL, et al: A phase II trial of interleukin-2 and interferon alfa-2a in patients with advanced renal cell carcinoma. J Clin Oncol 10:1124-1130, 1992

28. Motzer RJ, Nanus DM, O'Moore P, et al: Phase II trial of suramin in patients with advanced renal cell carcinoma: Treatment results, pharmacokinetics, and tumor growth factor expression. Cancer Res 52:5775-5779, 1992

29. Motzer RJ, Lyn P, Fischer P, et al: Phase I/II trial of dexverapamil plus vinblastine for patients with advanced renal cell carcinoma. J Clin Oncol 13:1958-1965, 1995

30. Law TM, Ilson DH, Motzer RJ: Phase II trial of topotecan in patients with advanced renal cell carcinoma. Invest New Drugs 12:143-145, 1994

31. Law TM, Mencel P, Motzer RJ: Phase II trial of liposomal encapsulated doxorubicin in patients with advanced renal cell carcinoma. Invest New Drugs 12:323-325, 1994

32. Motzer RJ, Murphy BA, Mazumdar M, et al: Randomized phase III trial of interferon alfa-2a (IFN) versus IFN plus 13-cis-retinoic acid (CRA) in patients (pts) with advanced renal cell carcinoma (RCC). Proc Am Soc Clin Oncol 18:330a, 1999 (abstr 1271)

33. Berg WJ, Schwartz LH, Amsterdam A, et al: A phase II study of 13-*cis*-retinoic acid in patients with advanced renal cell carcinoma. Invest New Drugs 15:353-355, 1997

34. Law TM, Motzer RJ, Minasian LM, et al: Risk stratification in advanced renal cell carcinoma: A single institution study of 237 patients. Proc Am Soc Clin Oncol 13:243, 1994 (abstr)

35. Orrell DH: Albumin as an aid to the interpretation of serum calcium. Clin Chim Acta 35:483-489, 1971

36. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. J Am Stat Assoc 53:457-481, 1958

37. Mantel N: Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemother Rep 50:163-170, 1966

38. Cox DR, Oakes D: Analysis of Survival Data. New York, Chapman and Hall, 1990

39. Gentlemen R, Crowley J: Graphical methods for censored data. J Am Stat Assoc 86:678-683, 1991

40. Heller G, Simonoff JS: Prediction in censored survival data: A comparison of the proportional hazards and linear regression models. Biometrics 48:101-115, 1992

41. Collet D: Modelling Survival Data in Medical Research. London, UK, Chapman and Hall, 1994

42. Mazumdar M, Glassman J: Categorizing a prognostic variable: Review of methods, codes for easy implementation and application to decision-making about cancer treatments. Stat in Med (in press)

43. Chen CH, George SL: The bootstrap and identification of prognostic factors via Cox's proportional hazards regression model. Stat Med 4:39-46, 1985

44. Sauerbrei W, Schumacher M: A bootstrap resampling procedure for model building: Application to the Cox regression model. Stat Med 11:2093-2109, 1992

45. Golimbu M, Joshi P, Sperber A: Renal cell carcinoma: Survival and prognostic factors. Urology 27:291-301, 1991

46. Maldazys JD, deKernion JB: Prognostic factors in renal cell carcinoma. J Urol 136:376-379, 1986

47. Thrasher JB, Paulson DF: Prognostic factors in renal cancer. Urol Clin North Am 20:247-261, 1993

48. Fossa S, Jones M, Joffe J, et al: Interferon-alpha and survival in renal cell cancer. Ann Oncol 76:286-290, 1995

49. Negrier S, Escudier B, Lasset C, et al: Recombinant human interleukin-2, recombinant human interferon alfa-2a, or both in metastatic renal-cell carcinoma. N Engl J Med 338:1273-1278, 1998

50. Neves RJ, Zincke H, Taylor WF: Metastatic renal cell cancer and radical nephrectomy: Identification of prognostic factor and patient survival. J Urol 139:1173-1176, 1988